ABBOTT

Corporate Regulatory Affairs

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August 30, 1999

The Food and Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane Room 1061
Rockville, MD 20857

RE: Draft Guidance for Industry - Changes to an Approved NDA or ANDA [Docket No. 99D-0529]

Dear Sirs or Madams:

Abbott Laboratories submits the following remarks in response to the Agency's request for comments on the above-named subject and docket. Abbott is an integrated worldwide manufacturer of healthcare products employing more than 56,000 people and serving customers in more than 130 countries.

I. GENERAL REMARKS

A. Overall delay. The guidance document is not as burdensome as the proposed rule which was published in the Federal Register on June 28, 1999. However, until the proposed rule has been processed through the comment and rulemaking period, we believe that finalizing this guidance document should be delayed until the various issues surrounding the proposed rule have been resolved. Specifically, if the current 21 CFR 314.70 lapses, we are unsure of the status, impact and procedures which would be in effect.

B. New requirements. While the draft guidance document reflects a high level of thought and effort by the Agency, in actuality the proposals add to the regulatory burdens placed on industry, which is contrary to the intent of FDAMA. While the new reporting category of *Changes Being Effected in 30 days* may provide some clarity to the general subject of change reporting, manufacturers are still left with new reporting conditions which were not required before.

99D-0529

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C. Relationship with Other Guidance Documents. The broad scope of this draft and the accompanying proposed rule brings in to question the relationship of this proposal with current guidance documents, as well as those guidances which are waiting to be finalized. For example, some additional detail should be provided regarding the stability guidance document and the guidance on container-closure systems. The relationship with the SUPAC and BACPAC documents should also be clarified.

II. SPECIFIC COMMENTS

A. Page 4, line 88. If making multiple manufacturing changes, it could be cumbersome to list all changes in a supplement cover letter, and especially in an annual report cover letter. A summary of the changes is typically included elsewhere in the supplement or annual report.

B. Page 8, line 239: It is not entirely clear what the reporting category should be for a change in manufacturing site for a container/closure component itself, such as a rubber stopper, a plastic port, a flexible container, etc. Some clarification would be desirable.

C. Page 10, line 285: Some of the 30-day CBE reporting categories appear to be more stringent than current annual report items, such as moving the manufacturing to a different room within the same facility. This also seems to be contradictory to page 11, line 319.

D. Page 13, line 395: Solution hold time validation changes may not have been interpreted by the industry as prior approval in the past, at least for terminally sterilized products. The Agency should reconsider this proposed section and allow for reporting under the CBE or annual reporting requirements. The rationale for this request is that this is a new requirement, the item is addressed at the plant level and it is routinely placed in validation packages.

E. Page 13, line 400: Filter materials and filter size changes are typically more relevant for aseptically filled products. Filter studies are typically kept at the manufacturing plants for pre-approval inspections for terminally sterilized drug products, rather than being included in the submission, as for aseptic products. The Agency should allow for a continued reporting at the plant level or through a reference in the annual report.

F. Page 15, line 445: Again, in-process filter changes are typically more relevant for aseptic products than for terminally sterilized products.

G. Page 16, line 494: "All changes" to specifications appears to be a stricter interpretation than what may have been interpreted in the past. At times, internal specification limits may be tightened for additional information only or to improve internal quality operations versus those contained in an already approved application.

H. Page 18, line 558: As in G, above, this appears to be a new requirement and differs with past Agency practices. Adding an additional, internal test may not have been formally reported in the past for an already approved application, unless it had to do with the safety or efficacy of the product.

I. Page 19, line 577: Per G and E above, a similar comment for internal tightening of acceptance criteria versus that in an already approved application.

J. Page 20, line 612: Does this paragraph indicate that a conversion to a composition already approved by CDER for similar products is not prior approval? Will an additive port reseal and/or an administration port cap composition change on flexible containers require prior approval for these types of changes in the future, since they are not primary packaging components?

K. Page 20, line 617: Similar comments: Does this indicate that a conversion to an ink and/or adhesive already approved by CDER for similar products is not prior approval?

L. Page 21, line 638: It may be useful to clarify changes in container size/shape as major versus minor for prior approval. For example, minor changes in a flexible container dimension (*i.e.*, tenths of an inch or so) should typically not have any significant impact on drug product stability.

M. Page 23, line 711: This appears to be a stricter reporting category for secondary packaging changes and should be allowed to be reported in an annual report. The draft verbiage already identifies this as "not intended to provide additional protection to the drug product."

N. Page 24, line 736: Exempted by regulation or guidance--does this need to be formally and explicitly stated in the regulation or guidance itself and which documents does this refer to? For example, changes to the storage conditions to match the draft FDA stability guideline--should this be exempted? What about after the guideline is finalized?

III. CLOSING COMMENTS

The proposed guidance should be revised and reissued as a proposed guidance for additional public comment for the following reasons:

A. The broad scope and potential impact on the industry.

B. Potential conflict with certain provisions of FDAMA. We are concerned about the overall regulations in effect if or when the current 21 CFR 314.70 lapses.

The Agency should conduct public meetings and/or sponsor a live telecast to review this proposed draft as well as the status and outcome of the existing regulations, the proposed regulations and the specific sections as defined in FDAMA.

Yours truly,

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cc: Nancy B. Sager (HFD-357)
[Docket No. 99N-0193]

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